Remarks

Claims 1, 5, 19, 21-27, 30, and 32-39 are pending in this application. Claims 5, 19, 22-23, 25-26 and 33 are amended to correct certain typographical errors. No new matter has been added.

Applicants appreciate the Examiner's withdrawal of the rejection under obviousness-type double patenting. Applicants respectfully submit that all of the pending claims are allowable for at least the following reasons.

A. The Pending Claims are Enabled

On pages 2-4 of the Office Action, the rejection of claims 25, 26, 36, and 37 as allegedly not enabled is maintained. In particular, it is alleged that the claims are not enabled because "while the specific diseases listed in [the claims] may be associated with TNFα, PDE4 and MMP activity, this does not provide enablement for those diseases and/or disorders ... claimed herein." (Office Action, page 2). Applicants respectfully traverse this rejection.

Again, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent, coupled with information known in the art, without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988) (emphasis added). The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Manual of Patent Examining Procedure* ("MPEP") § 2164.04 (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Accordingly:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must be taken as being in compliance with the enablement requirement* ... unless there is *a reason to doubt the objective truth of the statements* contained therein which must be relied on for enabling support
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> * * *
>
> It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to *explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its*

> *own with acceptable evidence or reasoning* which is inconsistent with the contested statement.

Id. (emphases added).

Initially, the Examiner alleges that "treatment of diseases based solely on their efficacious [sic] in inhibiting TNFα, PDE4 and MMP activity does not provide" enablement for the treatment of the diseases recited by the claims because "not all diseases and/or disorders are treatable." (Office Action, pages 2-3). However, the Examiner fails to provide any evidence that supports this allegation.[1] In other words, "the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention" by the Examiner has not been satisfied. For this reason alone, Applicants respectfully submit that this rejection should be withdrawn.

Applicants note that two references are provided in the Office Action in connection with the enablement rejection, *i.e.*, Borkakoti, *Progress in Biophysics and Molecular Biology*, 70: 73-94 (1998) ("Borkakoti") and Yu *et al.*, *Drug & Aging*, 11(3): 229-244 (1997) ("Yu"). Presumably, these references are provided to establish the reasonable basis to question the enablement of the claims. However, it is unclear how these references provide any reason to question the fact that the claims are enabled. Indeed, Applicants respectfully point out that these references actually support Applicants' position that the claims are enabled.

Borkakoti is an article directed to the review of structures of MMPs. Borkakoti clearly states that the excess synthesis and production of MMPs "lead to the accelerated matrix degradation associated with diseases such as arthritis, cancer and multiple sclerosis." (Borkakoti, Abstract). Borkakoti further states that "the control of MMP activity via safe, effective and specific low molecular weight inhibitors, therefore, provides potential as a new treatment for a variety of diseases." (*Id.*, pages 73-74). As the Examiner recognized in the Office Action, Borkakoti thus provides that MMP inhibitors "are being developed as potential treatment for disease conditions as diverse as cancer therapy, corneal ulceration and arthritis." (*Id.*, page 92; Office Action, page 3). Borkakoti goes on to state that such development activity "asserts the important role of MMPs in health and disease," implying that inhibition of MMPs was, at the time of this invention, considered by those of

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[1] Applicants note that two review articles (*i.e.*, Borkakoti and Yu) are provided in the Office Action in connection with this rejection. However, as discussed below, it is unclear how these references may provide "objective reason to doubt" the treatment of the diseases recited by the claims. (MPEP § 2164.04)

ordinary skill in the art to be an important avenue for the treatment of various diseases, *e.g.*, those recited by the pending claims. (Borkakoti, page 92). Therefore, none of the statements from Borkakoti are inconsistent with Applicants' submission that the diseases recited by the claims may be treated by the claimed pharmaceutical composition, and indeed, the disclosure of Borkakoti appears to support the fact that the claims are enabled.

Despite this fact, the Examiner alleges that because Borkakoti discloses that several inhibitors of MMPs are "being developed" for "potential therapy" for various diseases, "the uses being urged are not currently available form." (Office Action, page 4) (emphasis added). By this, the Examiner appears to be requiring that the treatment be "currently (commercially?) available" to be patentable. Applicants respectfully point out that such a proposition is legally incorrect.

In this regard, Applicants respectfully invite the Examiner's attention to *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), a copy of which is enclosed herein. In *Brana*, claims directed to the treatment of cancer were rejected as non-enabled based on certain references which, without questioning "the usefulness of any compounds as an antitumor agent," discussed the therapeutic value of the test disclosed in the specification. (*Brana*, 51 F.3d at 1566). In reversing the PTO's decision, the court first confirmed that the enablement cannot be questioned absent reason to doubt objective truth of the statements in the specification. (*Id.*, citing *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971)). Then, the court held that the burden of establishing the reason to doubt has not been established by the references cited by the examiner because the references, which merely discussed the therapeutic value of the test methods disclosed in the specification, are irrelevant for determining whether the claims are enabled. (*Id.*) This is because, the court held, such references are "relevant only if applicants must prove the ultimate value in humans of their asserted utility," but no such requirements exist for the treatment claims to be patentable. (*Id.*) (emphasis added).

Further, in discussing the enablement requirement in connection with pharmaceutical inventions, the court stated that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." (*Id.* at 1568) (emphasis added). The court further stated that since "[t]he stage at which an invention in [pharmaceutical] field becomes useful is well before it is ready to be administered to humans," requiring the proof of the ultimate value in humans of the asserted utility would "prevent many companies from obtaining patent

protection on promising new inventions, thereby eliminating an incentive to pursue ... potential cures in many crucial areas such as the treatment of cancer." (*Id.*).

The facts and holdings of *Brana* are directly applicable to the present application. As in *Brana*, Borkakoti does not provide any information whatsoever regarding usefulness of any compounds as therapies for any of the diseases, and merely discloses that many MMP inhibitors are currently being developed as potential therapies for various diseases.[2] As in *Brana*, the Examiner, by requiring that the asserted uses be "in currently available form," is essentially requiring that the proof of human efficacy be submitted to show the patentability of the claims. However, as the holdings of *Brana* make it clear, such requirement is legally unfounded, and the Examiner fails to establish her initial burden to question the enablement of the claims based on Borkakoti.

Applicants further submit that Yu, the second reference cited by the Examiner, also fails to provide any evidence that the claims are not enabled. As the Examiner recognizes, Yu discloses that MMPs are among "3 promising areas in which cancer biology research is likely to have an impact on therapeutics." (Yu, page 230; Office Action, page 3). Yu also discloses that "various synthetic MMP inhibitors have been shown to restrict tumour growth, and thus inhibit the process of tumour metastasis, in animal models of human diseases. (Yu, page 238). With regard to Batimastat, Yu discloses that possesses "ability to inhibit primary tumour growth, metastatic spread, and secondary tumour growth *in vivo*."[3] (*Id.*). Yu also discloses that "[i]nitial testing of lead MMP inhibitor compounds in various animal models of human cancer has suggested that [inhibition of MMPs] can delay primary tumour growth and limit tumour dissemination." (*Id.* at page 240). All of these statements evidence that the inhibition of MMPs was considered by those of ordinary skill in the art an

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[2] Indeed, Applicants point out that Borkakoti discloses much less than the references cited by the examiner in *Brana* because it does not even question the ultimate therapeutic value of MMP inhibitors. Quite to the contrary, Borkakoti clearly discloses that the inhibition of MMPs is an important avenue for the treatment of various diseases, as discussed above.

[3] Applicants note the Examiner's reference to the passage where it is disclosed that "treatment of batimastat did not cause any significant reduction in the number of metastases formed from a primary tumour." (Office Action, pages 3-4). However, closer reading of Yu reveals that batimastat, while it may provide no significant reduction in the number of metastases, significantly reduces the size of spontaneous metastases. (Yu, page 239). Thus, the passage referred to by the Examiner actually attests to the fact that batimastat may be effective in the treatment of cancer. More importantly, however, even assuming, *arguendo*, that Yu discloses that batimastat is unfit for the treatment of cancer, such a disclosure still does not provide any reason to question the enablement of the current claims, which recite the use of compounds different from batimastat.

important and plausible option for the treatment of cancer, and thus, Yu also supports Applicants' position with regard to the enablement of the current claims.

In sum, Applicants respectfully submit that: 1) the Examiner's reliance on Borkakoti and Yu is misplaced since these references fail to provide any evidence based on which the enablement of the current claims can be questioned; and 2) indeed, these references provide further support for Applicants' submission that the claims are enabled. For at least the foregoing reasons, Applicants respectfully request that the rejection of claims 25-26 and 36-37 under 35 U.S.C. § 112, ¶1 be withdrawn.

B. The Pending Claims Are Definite

On pages 4-5 of the Office Action, the rejection under 35 U.S.C. § 112, ¶2 with regard to claim 5 is maintained. In this regard, claim 5 is amended in this paper to correct the typographical errors pointed out by the Examiner. In view of these amendments, Applicants respectfully submit that the rejection of claim 5 be withdrawn.

On pages 5-6 of the Office Action, the rejection of claims 1, 5, 19, 21-27, 30, and 32-39 as allegedly indefinite is maintained. In particular, it is alleged that the claims are indefinite because "it is not known which diseases are capable of being responsive to the inhibition of TNFα, PDE4 and ... MMP activity," and the scope of diseases and/or disorders associated with the activity of TNFα, PDE4 and ... MMP could alter over time." (Office Action, page 6). It is further alleged that the claims are indefinite because "the claims are not directed to a method of treatment but to the method of inhibiting TNFα, PDE4 and ... MMP activity." (*Id.*). Applicants respectfully disagree with each of these allegations.

With regard to rejections under 35 U.S.C. § 112, ¶2, it is well-settled that "the primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claim is clear so that public is informed of the boundaries of what constitutes infringement of the patent." (*Manual of Patent Examining Procedure* ("MPEP"), § 2173). Accordingly:

> If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

(*Id.*, § 2173.04 (emphasis added)).

Applicants respectfully submit that the pending claims are definite because "the scope of the subject matter embraced by the claims is clear." (*Id.*). The pending claims are directed, in part, to: 1) compositions for, and methods of reducing the levels of TNFα, PDE4 or MMP; and 2) the treatment of specifically recited diseases. With regard to the claims directed to reducing the levels of TNFα, PDE4 or MMP, Applicants respectfully point out that there is no question as to what the subject matter embraced by the claims is. In other words, the specification clearly states that the compounds recited by these claims are effective in reducing the levels of TNFα, PDE4 or MMP,[4] which is precisely the subject matter recited by these claims. It is unclear why "what biological system or physiological effect [the reduction of TNFα, PDE4 or MMP] pertains" must be known for these claims to be definite. (Office Action, page 6). Clearly, those of ordinary skill in the art would have no uncertainty whatsoever in determining what the term "reducing the level of TNFα, PDE4 or MMP" means without knowing the "biological system" or "physiological effect" to which this reduction pertains.

Further, there is also no uncertainty in determining the scope of the claims directed to the treatment of specific diseases. This is because these claims recite the treatment of specific diseases, which are expressly listed in the specification and well-known to those of ordinary skill in the art, using specific compounds, which are described in detail in the specification. Clearly, there can be no question as to the scope of these claims, and thus, these claims are also definite.[5]

In sum, Applicants respectfully submit that the pending claims are definite because there is no uncertainty as to what subject matter is embraced by the pending claims. Thus, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, ¶2 be withdrawn.

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[4] Although not required, the efficacy of the compounds recited by the pending claims is evidenced, for example, by the IC_{50} data submitted in Applicants' previous response. (*See* Applicants' Response of September 2, 2005, pages 12-15).

[5] To the extent that the Examiner may be alleging that the claims are indefinite because those of ordinary skill in the art may have to test each of the compounds for their efficacy in treating a specific disease, Applicants respectfully point out that: 1) the Examiner does not provide any evidence that such tests are necessary; and 2) such an allegation is irrelevant to the assessment of claim definiteness as the pending claims have a well-defined scope as discussed above. Even assuming, *arguendo*, such tests are somehow required for those of ordinary skill in the art to determine the scope of the pending claims, Applicants point out that such tests are routine in the art and not undue. (*See, e.g., Ex Parte Skuballa*, 12 U.S.P.Q.2d 1570, 1571 (B.P.A.I., 1989)).

Conclusion

In view of the foregoing, Applicants respectfully submit that all of the pending claims are allowable, and thus request the rejection of the claims be withdrawn.

No fee is believed due for the submission of this paper. If any fees are required for the submission of this paper, or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date: February 28, 2006

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United States Court of Appeals,Federal Circuit.
In re Miguel F. BRANA, Jose M.C. Berlanga, Marina M. Moset, Erich Schlick and Gerhard Keilhauer.
93-1393.

March 30, 1995.

Applicants appealed from decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences, affirming patent examiner's rejections of claims for antitumor compound. The Court of Appeals, Plager, Circuit Judge, held that: (1) claimed specification for antitumor compound satisfied statutory utility requirement by alleging that compound was more effective in treating lymphocytic leukemia in mice than other known compounds; (2) PTO failed to satisfy its initial burden of challenging presumptively correct assertion of utility; (3) even if one skilled in the art would have reasonably questioned asserted utility of claimed antitumor compound, applicants provided sufficient evidence to convince one of skill in the art of asserted utility; and (4) Food and Drug Administration (FDA) approval is not prerequisite for finding compound useful within meaning of patent laws.

Reversed.

West Headnotes

[1] **Patents 291 ⚿101(5)**

291 Patents
291IV Applications and Proceedings Thereon
291k101 Claims
291k101(5) k. Requisites and Sufficiency. Most Cited Cases
Claim specifications for antitumor compound satisfied statutory utility requirement by alleging that compound was more effective in treating lymphocytic leukemia in mice than other known compounds. 35 U.S.C.A. § 101.

[2] **Patents 291 ⚿48**

291 Patents
291II Patentability
291II(C) Utility
291k48 k. Nature of Product or Result. Most Cited Cases
Lymphocytic leukemia tumor models used to study cancer in mice represented specific diseases against which claimed compounds in patent application could be effective, as required to satisfy statutory utility requirement, where cell lines used on models were originally derived from lymphocytic leukemias in mice and would produce that disease once implanted in mice. 35 U.S.C.A. § 101.

[3] **Patents 291 ⚿97**

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Patent and Trademark Office (PTO) has initial burden of challenging presumptively correct assertion of utility in patent disclosure. 35 U.S.C.A. § 101.

[4] **Patents 291 ⚿97**

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Only after Patent and Trademark Office (PTO) provides evidence showing that one of ordinary skill in art would reasonably doubt asserted utility of patented invention does burden shift to applicant to provide rebuttal evidence sufficient to convince such person of invention's asserted utility. 35 U.S.C.A. § 101.

[5] **Patents 291 ⚿97**

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Patent and Trademark Office (PTO) failed to satisfy its initial burden of challenging presumptively correct assertion of utility in application for patent for antitumor compound, where references cited by PTO did not question usefulness of any compound as antitumor agent or provide any other evidence to cause one of skill in the art to question asserted utility of applicants' compounds, but instead discussed therapeutic predictive value of tests used in mice, which were relevant only if applicants were required

to prove ultimate value in humans of their asserted utility. 35 U.S.C.A. § 101.

[6] **Patents 291 99**

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
Even if one skilled in the art would have reasonably questioned asserted utility of claimed antitumor compound, applicants provided sufficient evidence to convince one of skill in the art of asserted utility; applicants provided test results showing that several compounds within scope of claims exhibited significant antitumor activity, and prior art disclosed structurally similar compounds which were proven to be effective antitumor agents. 35 U.S.C.A. § 101.

[7] **Patents 291 49**

291 Patents
291II Patentability
291II(C) Utility
291k49 k. Evidence of Utility. Most Cited Cases
Although minor changes in chemical compounds can radically change their effects on human body, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe asserted utility.

[8] **Patents 291 46**

291 Patents
291II Patentability
291II(C) Utility
291k46 k. Nature and Necessity of Patentable Utility. Most Cited Cases
Food and Drug Administration (FDA) approval is not prerequisite for finding compound useful within meaning of patent laws. Federal Food, Drug, and Cosmetic Act, § 505(i)(1), 21 U.S.C.A. § 355(i)(1); 35 U.S.C.A. § § 101, 112; 21 C.F.R. § § 312.21(b), 312.23(a)(5), (a)(8).

[9] **Patents 291 324.5**

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.5 k. Scope and Extent of Review in General. Most Cited Cases
In reviewing decisions of Patent and Trademark Office (PTO), Court of Appeals traditionally reviews questions of law without deference to views of the agency, and defers to agency with regard to questions of fact unless its findings are clearly erroneous.

[10] **Patents 291 324.55(1)**

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.55 Questions of Fact, Verdicts, and Findings
291k324.55(1) k. In General. Most Cited Cases
When mixed questions of law and fact are before Court of Appeals on appeal from decision of Patent and Trademark Office (PTO), whether Court of Appeals defers, and extent to which it defers to agency's decision, turns on nature of case and nature of judgment. 5 U.S.C.A. § 706.

***1562** Malcolm J. MacDonald, Keil & Weinkauf, Washington, DC, argued, for appellant. With him on the brief was Herbert B. Keil. Of counsel was David S. Nagy.
Fred E. McKelvey, Sol., Office of Sol., Arlington, VA, argued, for appellee. With him on the brief were Albin F. Drost, Deputy Sol., Richard E. Schafer, Teddy S. Gron, Joseph G. Piccolo and Richard L. Torczon, Associate Sols.

Before PLAGER, LOURIE, and RADER, Circuit Judges.

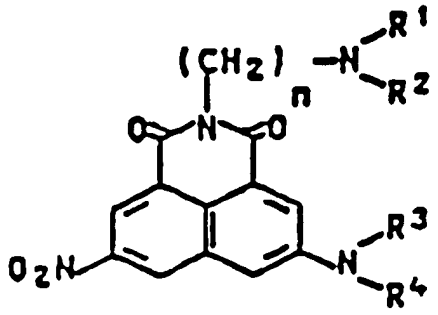
PLAGER, Circuit Judge.
Miguel F. Brana, *et al.* (applicants), appeal the March 19, 1993 decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), in Appeal No. 92-1196. The Board affirmed the examiner's rejection of claims 10-13 of patent application Serial No. 533,944 under 35 U.S.C. § 112 ¶ 1 (1988). [FN1] The examiner's rejection, upon which the Board relied in rendering its decision, was based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation necessary to use the compounds. We conclude the Board erred, and reverse.

FN1. Unless otherwise noted, all United States Code citations are to the 1988 edition.

I. BACKGROUND

On June 30, 1988, applicants filed patent application Serial No. 213,690 (the '690 application) [FN2] directed to 5-nitrobenzo[de]isoquinoline-1,3-dione compounds, for use as antitumor substances, having the following formula:

FN2. This is a divisional of patent application Serial No. 110,871 filed October 21, 1987.



where n is 1 or 2, R^1 and R^2 are identical or different and are each hydrogen, C1-C6-alkyl, C1-C6-hydroxyalkyl, pyrrolidinyl, morpholino, piperidinyl or piperacinyl, and R^3 and R^4 are identical or different and are each hydrogen, C1-C6-alkyl, C1-C6-acyl, C2-C7-alkoxycarbonyl, ureyl, aminocarbonyl or C2-C7-alkylaminocarbonyl. These claimed compounds differ from several prior art benzo[de]isoquinoline-1,3-dione compounds due to the presence of a nitro group (O2N) at the 5-position and an amino or other amino group (NR^3R^4) at the 8-position of the isoquinoline ring.

The specification states that these non-symmetrical substitutions at the 5-and 8-positions produce compounds with "a better action and a better action spectrum as antitumor substances" than known benzo[de]isoquinolines, namely those in K.D. Paull et al., *Computer Assisted Structure-Activity Correlations,* Drug Research, 34(II), 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo[de]isoquinoline-1,3-diones and related compounds which have been screened for antitumor activity by testing their efficacy ***in vivo*** [FN3] against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. [FN4] These two ***in vivo*** tests are ***1563** widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Paull noted that one compound in particular, benzo[de]isoquinoline-1,3(2H)dione,5-amino-2(2-di methyl-aminoethyl [sic]) (hereinafter "NSC 308847"), was found to show excellent activity against these two specific tumor models. Based on their analysis, compound NSC 308847 was selected for further studies by NCI. In addition to comparing the effectiveness of the claimed compounds with structurally similar compounds in Paull, applicants' patent specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, ***in vitro,*** [FN5] and concludes that these tests "had a good action." [FN6]

FN3. ***In vivo*** means "[i]n the living body, referring to a process occurring therein." Steadman's Medical Dictionary 798 (25th ed. 1990). ***In vitro*** means "[i]n an artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media." *Id.*

FN4. The analysis in Paull consisted of grouping the previously-tested compounds into groups based on common structural features and cross-referencing the various groups, in light of the success rates of the group as a whole, to determine specific compounds that may be effective in treating tumors.

FN5. *See supra* note 3.

FN6. The specification does not state the specific type of human tumor cells used in this test.

The examiner initially rejected applicants' claims in the '690 application as obvious under 35 U.S.C. § 103 in light of U.S. Patent No. 4,614,820, issued to and referred to hereafter as Zee-Cheng et al. Zee-Cheng et al. discloses a benzo[de]isoquinoline compound for use as an antitumor agent with symmetrical substitutions on the 5-position and 8-position of the quinoline ring; in both positions the substitution was either an amino or nitro group. [FN7] Although not identical to the applicants' claimed compounds, the examiner noted the similar substitution pattern (i.e., at the same positions on the isoquinoline ring) and concluded that a mixed substitution of the invention therefore would have been obvious in view of Zee-Cheng et al.

FN7. The chemical compound in Zee-Cheng et al. is labeled a 3,6-disubstituted-1,8-naphthalimide and uses

> different numbering for the positions on the isoquinoline ring. The structure of this compound, however, is identical to that claimed by the applicants except for symmetrical substitutions at the 5-position and the 8-position of the isoquinoline ring. Zee-Cheng et al. teaches identical substitutions of amino or nitro groups while applicants claim a nitro group substitution at the 5-position and an amino group substitution at the 8-position.

In a response dated July 14, 1989, the applicants rebutted the § 103 rejection. Applicants asserted that their mixed disubstituted compounds had unexpectedly better antitumor properties than the symmetrically substituted compounds in Zee-Cheng et al. In support of this assertion applicants attached the declaration of Dr. Gerhard Keilhauer. In his declaration Dr. Keilhauer reported that his tests indicated that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in Zee-Cheng et al. when tested, ***in vitro,*** against two specific types of human tumor cells, HEp and HCT-29. [FN8] Applicants further noted that, although the differences between the compounds in Zee-Cheng et al. and applicants' claimed compounds were slight, there was no suggestion in the art that these improved results (over Zee-Cheng et al.) would have been expected. Although the applicants overcame the § 103 rejection, the examiner nevertheless issued a final rejection, on different grounds, on September 5, 1989.

> FN8. HEp cells are derived from laryngeal cancer and HCT-29 cells from colon cancer.

On June 4, 1990, applicants filed a continuation application, Serial No. 533,944 (the '944 application), from the above-mentioned '690 application. Claims 10-13, the only claims remaining in the continuation application, were rejected in a final office action dated May 1, 1991. Applicants appealed the examiner's final rejection to the Board.

In his answer to the applicants' appeal brief, the examiner stated that the final rejection was based on 35 U.S.C. § 112 ¶ 1. [FN9] The examiner first noted that the specification failed to describe any specific disease against which the claimed compounds were active. Furthermore, the examiner concluded that the prior art tests performed in Paull and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had ***1564** a practical utility (i.e. antitumor activity in humans). [FN10]

> FN9. The examiner's answer noted that the final rejection also could have been made under 35 U.S.C. § 101 for failure to disclose a practical utility.

> FN10. The examiner subsequently filed two supplemental answers in response to arguments raised by the applicants in supplemental reply briefs.

In a decision dated March 19, 1993, the Board affirmed the examiner's final rejection. The three-page opinion, which lacked any additional analysis, relied entirely on the examiner's reasoning. Although noting that it also would have been proper for the examiner to reject the claims under 35 U.S.C. § 101, the Board affirmed solely on the basis of the Examiner's § 112 ¶ 1 rejection. This appeal followed.

II. DISCUSSION

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. [FN11] We note the Commissioner has recently addressed this question in his Examiner Guidelines for Biotech Applications, *see* 60 Fed.Reg. 97 (1995); 49 Pat.Trademark & Copyright J. (BNA) No. 1210, at 234 (Jan. 5, 1995).

> FN11. *See, e.g., Cross v. Iizuka,* 753 F.2d 1040, 224 USPQ 739 (Fed.Cir.1985); *In re Langer,* 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Krimmel,* 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961).

The requirement that an invention have utility is found in 35 U.S.C. § 101: "Whoever invents ... any new and *useful* ... composition of matter ... may obtain a patent therefor...." (emphasis added). It is also implicit in § 112 ¶ 1, which reads:
The specification shall contain a written description of

the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it.

As noted, although the examiner and the Board both mentioned § 101, and the rejection appears to be based on the issue of whether the compounds had a practical utility, a § 101 issue, the rejection according to the Board stands on the requirements of § 112 ¶ 1. It is to that provision that we address ourselves. [FN12] The Board gives two reasons for the rejection; [FN13] we will consider these in turn.

FN12. This court's predecessor has determined that absence of utility can be the basis of a rejection under both 35 U.S.C. § 101 and § 112 ¶ 1. *In re Jolles*, 628 F.2d 1322, 1326 n. 11, 206 USPQ 885, 889 n. 11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) ("[I]f such compositions are in fact useless, appellant's specification cannot have taught how to use them."). Since the Board affirmed the examiner's rejection based solely on § 112 ¶ 1, however, our review is limited only to whether the application complies with § 112 ¶ 1.

FN13. The Board's decision did not expressly make any independent factual determinations or legal conclusions. Rather, the Board stated that it "agree[d] with the examiner's well reasoned, well stated and fully supported by citation of relevant precedent position in every particular, and any further comment which we might add would be redundant." *Ex parte Brana et al.*, No. 92-1196 (Bd.Pat.App. & Int. March 19, 1993) at 2-3. Therefore, reference in this opinion to Board findings are actually arguments made by the examiner which have been expressly adopted by the Board.

1.

[1] The first basis for the Board's decision was that the applicants' specification failed to disclose a specific disease against which the claimed compounds are useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed.Cir.1986), *cert. denied*, 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). In support, the Commissioner argues that the disclosed uses in ***1565** the '944 application, namely the "treatment of diseases" and "antitumor substances," are similar to the nebulous disclosure found insufficient in *In re Kirk*, 376 F.2d 936, 153 USPQ 48 (CCPA 1967). This argument is not without merit.

In *Kirk* applicants claimed a new class of steroid compounds. One of the alleged utilities disclosed in the specification was that these compounds possessed "high biological activity." *Id.* at 938, 153 USPQ at 50. The specification, however, failed to disclose which biological properties made the compounds useful. Moreover, the court found that known specific uses of similar compounds did not cure this defect since there was no disclosure in the specification that the properties of the claimed compounds were the same as those of the known similar compounds. *Id.* at 942, 153 USPQ at 53. Furthermore, it was not alleged that one of skill in the art would have known of any specific uses, and therefore, the court concluded this alleged use was too obscure to enable one of skill in the art to use the claimed invention. *See also Kawai v. Metlesics*, 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

Kirk would potentially be dispositive of this case were the above-mentioned language the only assertion of utility found in the '944 application. Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, *see supra* note 4, Paull grouped various benzo[de]isoquinoline-1,3-diones, which had previously been tested *in vivo* for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, [FN14] applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more

specific than the vaguely intimated uses rejected by the courts in *Kirk* and *Kawai*. *See, e.g.*, Cross v. Iizuka, 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds-the inhibition of thromboxane synthetase in human or bovine platelet microsomes-sufficiently specific to satisfy the threshold requirement in *Kirk* and *Kawai*.)

FN14. Paull also found NSC 308847 to be effective against two other test models, B16 melanoma and Colon C872.

[2] The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor ***in vivo***, as would be implied from the Commissioner's argument, there would be no effective way to test compounds ***in vivo*** on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use.

2.

[3] [4] The second basis for the Board's rejection was that, even if the specification did allege a specific use, applicants failed to ***1566** prove that the claimed compounds are useful. Citing various references, FN15 the Board found, and the Commissioner now argues, that the tests offered by the applicants to prove utility were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. FN16

FN15. *See* Pazdur et al., *Correlation of Murine Antitumor Models in Predicting Clinical Drug Activity in Non-Small Cell Lung Cancer: A Six Year Experience*, 3 Proceedings Am.Soc.Clin.Oncology 219 (1984); Martin et al., *Role of Murine Tumor Models in Cancer Research*, 46 Cancer Research 2189 (April 1986).

FN16. As noted, this would appear to be a § 101 issue, rather than § 112.

This court's predecessor has stated:
[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy*, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981). FN17

FN17. *See also In re Novak*, 306 F.2d 924, 928, 134 USPQ 335, 337 (CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky*, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956) ("[W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry ... no further evidence is required."). *But see In re Marzocchi*, 439 F.2d at 223, 169 USPQ at 369-70 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad

> statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles.").

[5] The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, FN18 do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests-relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness.

FN18. *See supra* note 15.

The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles*, 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng et al., discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.

Taking these facts-the nature of the invention and the PTO's proffered evidence-into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112. *See In re Marzocchi*, 439 F.2d at 224, 169 USPQ at 370.

[6] We do not rest our decision there, however. Even if one skilled in the art ***1567** would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility. In particular, applicants provided through Dr. Kluge's declaration FN19 test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor model ***in vivo.*** Such evidence alone should have been sufficient to satisfy applicants' burden.

FN19. The declaration of Michael Kluge was signed and dated June 19, 1991. This declaration listed test results (i.e. antitumor activity) of the claimed compounds, *in vivo,* against L1210 tumor cells and concluded that these compounds would likely be clinically useful as anti-cancer agents. Enablement, or utility, is determined as of the application filing date. *In re Glass*, 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi*, 439 F.2d at 224 n. 4, 169 USPQ at 370 n. 4. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

[7] The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility. As previously mentioned, prior art-Zee Cheng et al. and Paull-disclosed structurally similar compounds which were proven ***in vivo*** against various tumor models to be effective as chemotherapeutic agents. Although it is true that minor changes in chemical compounds can radically alter their effects on the human body, *Kawai*, 480 F.2d at 891, 178 USPQ at 167, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility. *See Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); *Kawai*, 480 F.2d 880, 178 USPQ 158.

The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. FN20 The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed.Cir.1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly

left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

> FN20. We note that this discussion is relevant to the earlier discussion as well. If we were to conclude that these *in vivo* tests are insufficient to establish usefulness for the claimed compounds, that would bear on the issue of whether one skilled in the art would, in light of the structurally similar compounds in Paull and Zee Cheng et al., have cause to doubt applicants' asserted usefulness for the compounds.

Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *see also In re Bergel*, 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated:

We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans.

Krimmel, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new ***1568** compounds may be useful as antitumor agents.

In the context of this case the Martin and Pazdur references, on which the Commissioner relies, do not convince us otherwise. Pazdur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of ***in vivo*** murine tumor models for human therapy, Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e. lack of predictive reliability) is not tenable in light of present information.

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. § 355(i)(1); 21 C.F.R. § 312.23(a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. § 312.21(b).

[8] FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. § 112 ¶ 1.

3.

[9] The Commissioner takes this opportunity to raise the question of this court's standard of review when deciding cases on appeal from the PTO. Traditionally we have recited our standard of review to be, with regard to questions of law, that review is without deference to the views of the Agency, *In re Donaldson*, 16 F.3d 1189, 1192, 29 USPQ2d 1845, 1848 (Fed.Cir.1994) (in banc), *In re Caveney*, 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed.Cir.1985), and with regard to questions of fact, we defer to the Agency unless its findings are "clearly erroneous." *See, e.g., In re Baxter Travenol Labs*, 952 F.2d 388, 21 USPQ2d 1281 (Fed.Cir.1991); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir.1990); *In re De Blauwe*, 736 F.2d 699, 222 USPQ 191 (Fed.Cir.1984).

[10] With regard to judgment calls, those questions

that fall "[s]omewhere near the middle of the fact-law spectrum," this court has recognized "the falseness of the fact-law dichotomy, since the determination at issue, involving as it does the application of a general legal standard to particular facts, is probably most realistically described as neither of fact nor law, but mixed." *Campbell v. Merit Systems Protection Board*, 27 F.3d 1560, 1565 (Fed.Cir.1994). When these questions of judgment are before us, whether we defer, and the extent to which we defer, turns on the nature of the case and the nature of the judgment. *Id.* ("Characterization therefore must follow from an *a priori* decision as to whether deferring ... is sound judicial policy. We would be less than candid to suggest otherwise.").

The Commissioner contends that the appropriate standard of review for this court regarding questions of law, of fact, and mixed questions of law and fact, coming to us from the PTO is found in the Administrative Procedure Act (APA) at 5 U.S.C. § 706. The standard set out there is that "[t]he reviewing court shall ... hold unlawful and set aside agency action, findings, and conclusions found to be-(A) arbitrary, capricious, an ***1569** abuse of discretion, or otherwise not in accordance with law; ... (E) unsupported by substantial evidence...." The Commissioner is of the view that the stated standard we now use, which is the traditional standard of review for matters coming from a trial court, is not appropriate for decisions coming from an agency with presumed expertise in the subject area, and is not in accord with law. [FN21]

> FN21. Congress enacted the Administrative Procedure Act (APA) on June 11, 1946. *See* 1 Kenneth Culp Davis, Administrative Law Treatise, § 1:7 (2d ed. 1978). The APA sets forth a framework for administrative agency procedure and provides judicial review for persons adversely affected by final agency actions. Chapter 7, codified at 5 U.S.C. § 701-706, contains the APA judicial review provisions, including the standard of review provision quoted above.

Applicants argue that by custom and tradition, recognized by the law of this court, the standard of review we have applied, even though inconsistent with the standard set forth in the APA, nevertheless is a permissible standard. In our consideration of this issue, there is a reality check: would it matter to the outcome in a given case which formulation of the standard a court articulates in arriving at its decision? The answer no doubt must be that, even though in some cases it might not matter, in others it would, otherwise the lengthy debates about the meaning of these formulations and the circumstances in which they apply would be unnecessary.

A preliminary question, then, is whether this is one of those cases in which a difference in the standard of review would make a difference in the outcome. The ultimate issue is whether the Board correctly applied the § 112 ¶ 1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of § 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

III. CONCLUSION

The Board erred in affirming the examiner's rejection under 35 U.S.C. § 112 ¶ 1. The decision is reversed.

REVERSED.

C.A.Fed.,1995.
In re Brana
51 F.3d 1560, 34 U.S.P.Q.2d 1436, 63 USLW 2656

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